complexes at least $1x10^6$. Support for the claim language appears at page 20, line3 and page 17, line 7.

In contrast, the primary reference cited, Motwani et al., merely teaches a yeast system for expressing a functional heterologous multi-domain protein, such as **an antibody**. This reference teaches using a single vector that includes multiple expression cassettes to express "equivalent amounts of the multiple polypeptide chains, thereby enhancing the yield of a functional heterologous multi-domain protein". See "Abstract" and Summary of the Invention" at column 6, lines 41-64. Nowhere in this reference could be found a teaching or suggestion of constructing a library of yeast expression vectors for expression a highly ($\geq 1x10^6$) diverse library of protein complexes as specified in claim 54.

The secondary reference cited, Fusco et al., teaches a method of constructing a cDNA library for use in the yeast two-hybrid system. Specifically, a cDNA library such as Marathon-Ready (from Clontech) (page 718, column 1, lines 2-3) and one derived from mRNA of the substantia nigra of human brain (page 718, column 2, lines 11-13). The cDNA library was cloned into a **single**, linearized expression vector containing a GAL1 promoter (pJG4-5, page 717, column 1, last paragraph, lines 1-3). The diversity of the human brain cDNA library is at most $5x10^5$. This reference does not teach a method of transforming **a library of insert nucleotides (encoding V_2 library)** and **a library of linearized expression vectors (encoding V_1 library)** into yeast to produce a library of protein complexes (**V_1/V_2 complexes**) with at least $1x10^6$ diversity. Thus, Fusco et al. does not teach constructing a library of expression vectors encoding protein complexes, let alone suggesting constructing such a library with high diversity as specified in claim 54.

To establish a prima facie case of obviousness, the Examiner bears the burden of proving 1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; 2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success of the claimed invention. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

First, the Examiner has not made a showing that the prior art cited, Motwani et al. and Fusco et al. combined, teaches or suggests all the claim limitations. As discussed in detail above, Motwani et al. teaches a method of constructing a single vector that includes multiple expression cassettes to express a functional monoclonal antibody; wherein Fusco et al. teaches constructing yeast expression vectors encoding a cDNA library. Neither Motwani et al. nor Fusco et al. teaches or suggests a method of transforming V_2 library and a library of linearized expression vectors encoding a V_1 library with diversity of at least $1x10^3$ into yeast to produce a

library of V_1/V_2 complexes with at least $1x10^6$ diversity.

Second, the Examiner has not presented an objective reason why one of ordinary skill in the art would be motivated to modify Motwani et al. in view of Fusco et al. As stated in its abstract, Motwani et al. focuses on constructing a single plasmid containing twin cassette in order to ensure production of multiple chains in equivalent amounts and in high yield. This reference neither concerns about the efficiency problem of constructing a library of expression vectors in yeast nor suggests a solution to it.

On the other hand, Fusco et al. merely teaches a general method of how to clone a cDNA library into a **single, linearized expression vector** via homologous recombination in yeast. Nowhere in this reference teaches or suggests that a cDNA library could be cloned into **a library of expression vectors** to produce a library of protein complexes. Absent any showing of objective evidence, this gap cannot be filled by simply taking a notice that one of ordinary skill in the art is motivated to modify Motwani et al. in view Fusco.

In view of the failure of the cited reference to teach or suggest all of the elements recited in independent claims and the lack of motivation to modify Motwani et al. to arrive the daimed invention, the Examiner has failed to establish a prima facie case of obviousness under 35 U.S.C. 103(a). Withdrawal of this ground of rejection is therefore respectively requested.

II. Obviousness Rejection under 35 U.S.C. §103 over Motwani et al. and Kostrub et al.

The Examiner also rejects claims 54-61 under 35 U.S.C. § 103(a) as being unpatentable over Motwani et al. and Kostrub et al. (1998) Nudeic Acid Res. 26:4783-4784.

Similar to Fusco et al., Kostrub et al., teaches a method of cloning a library of mutants into a **single, linearized expression vector** via homologous recombination in yeast. Page 1, Abstract, line 4. Nowhere in this reference teaches or suggests that a mutant library could be cloned into a **library of expression vectors** to produce a library of protein complexes.

As discussed in detail above, neither Motwani et al. Kostrub et al. teaches or suggests a method of transforming V_2 library and a library of linearized expression vectors encoding a V_1 library with diversity of at least $1x10^3$ into yeast to produce a library of V_1/V_2 complexes with at least $1x10^6$ diversity.

In view of the failure of the cited reference to teach or suggest all of the elements recited in independent claims and the lack of motivation to modify Motwani et al. to arrive the daimed invention, the Examiner has failed to establish a prima facie case of obviousness under 35 U.S.C. 103(a). Withdrawal of this ground of rejection is therefore respectively requested.

CONCLUSION

In light of the remarks and arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Date: Aug. 6, 2002

By: _____
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